New insights into thyroid cancer epidemiology: Chernobyl, Fukushima and beyond

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outline

• radiation and thyroid cancer: lessons from Chernobyl:
  - internal vs. irradiation external
  - latency
  - potential risk modifiers (host and environmental)
  - exposure in childhood vs. adulthood

• role of increased surveillance:
  - Chernobyl, Fukushima and beyond…

• summary
external irradiation: A bomb survivors

• shorter latency compared to other radiation induced solid cancers - (apparent from 5 years after exposure)
• risks decrease with increasing age at exp. (31% decrease in risk with increasing decade of age at exp.)*
• linear dose response but suggestion of downward curvature above 2 Gy**
• females having higher risks: ERR/1 Gy sex ratio F:M 1.3 (95%CI: 0.56-3.9)*
• risk persists >50 years after exposure but decreases with attained age **

*Preston et al, 2007
**Furukawa et al, 2013
Chernobyl: external irradiation vs. internal

- first reports on thyroid cancer increase after Chernobyl were met with scepticism because:
  - susceptibility of thyroid gland to internal exposure from radioactive iodine was less established, compared to external radiation exposure
  - main evidence came from studies of medically exposed populations with underlying thyroid conditions and limited data on childhood exposure
Chernobyl: latency

• very early onset (first cases appeared only 3 to 4 years after the accident) was unexpected based on existing knowledge from externally exposed populations*

Caution: the first cases demonstrated very clear clinical symptoms, they were not detected by screening

* Ron et al, 1995; Veiga et al, 2016

Photo: http://renaissanceresearch.blogspot.fr/2006_04_01_archive.html
# Chernobyl: risks after exposure in childhood and adolescence

## Summary of most informative analytical studies

<table>
<thead>
<tr>
<th>Study</th>
<th>Ascertainment period</th>
<th>Number of cases</th>
<th>Number of controls/size of study population/PY</th>
<th>ERR* at 1 Gy (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Chernobyl studies</strong></td>
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<tr>
<td><em>Case-control studies</em></td>
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<tr>
<td>Astakhova <em>et al</em>, 1998</td>
<td>1988-1992</td>
<td>107</td>
<td>214</td>
<td>OR &gt;=1 Gy vs. &lt;0.3Gy: 5.0 (1.5-16.7) to 5.8 (2.0-17.3)</td>
</tr>
<tr>
<td>Cardis <em>et al</em>, 2005</td>
<td>1992-1998</td>
<td>276</td>
<td>1,300</td>
<td>4.5 (2.1-8.5) to 7.4 (3.1-16.3)</td>
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<tr>
<td><strong>Screened cohort study</strong></td>
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<tr>
<td>Tronko <em>et al</em>, 2006</td>
<td>1998-2000</td>
<td>45</td>
<td>13,127</td>
<td>5.25 (1.7-25.5)</td>
</tr>
<tr>
<td>Brenner <em>et al</em>, 2011</td>
<td>2001-2007</td>
<td>65</td>
<td>12,514</td>
<td>1.91 (0.43–6.34)</td>
</tr>
<tr>
<td>Zablotska <em>et al</em>, 2010</td>
<td>1996-2004</td>
<td>133</td>
<td>11,611</td>
<td>3.16 (1.49 – 6.95)</td>
</tr>
<tr>
<td>Hatch <em>et al</em>, 2009</td>
<td>2003-2006</td>
<td>7</td>
<td>2,582</td>
<td>11.7 (NE – 1,982)</td>
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<tr>
<td><strong>Exposure in utero</strong></td>
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<tr>
<td>Ron <em>et al</em>, 1995</td>
<td></td>
<td></td>
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<td>7.7 (2.1-28.7)</td>
</tr>
<tr>
<td>Veiga <em>et al</em>, 2016</td>
<td></td>
<td></td>
<td></td>
<td>5.5 (4.1-7.5)</td>
</tr>
</tbody>
</table>

*ERR=excess relative risk
Chernobyl: effect modifiers

- age at exposure and gender

<table>
<thead>
<tr>
<th>Reference</th>
<th>Ratio ERR/Gy girls/boys</th>
<th>Age at exposure effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardis et al, 2005</td>
<td>0.9, p=0.9</td>
<td>NA</td>
</tr>
<tr>
<td>Kopecky et al, 2006</td>
<td>NA</td>
<td>No monotone trend with increasing age; p=0.7</td>
</tr>
<tr>
<td>Tronko et al, 2006</td>
<td>7.5, p=0.14</td>
<td>ERR decreased with increasing age at exposure; p=0.6</td>
</tr>
<tr>
<td>Brenner et al, 2011</td>
<td>2.2, p=0.9</td>
<td>ERR decreased with increasing age at exposure; p=0.4</td>
</tr>
<tr>
<td>Zablotska et al, 2010</td>
<td>3.0, p=0.13</td>
<td>No significant effect of age at exposure; p=0.9</td>
</tr>
<tr>
<td>Ron et al, 1995</td>
<td>2, p=0.07</td>
<td>ERR decreased with increasing age at exposure; p=0.004</td>
</tr>
<tr>
<td>Veiga et al, 2016</td>
<td>0.8, p=0.37</td>
<td>ERR varied significantly with age at exposure; p=0.001</td>
</tr>
</tbody>
</table>

- effect of gender not clear because most of TC diagnosed at very young age (mean age ATD-11.7 (Demidchik et al 2006))
  - overall, risk decreases with increasing age at exp. although trends are not always significant or monotonous
Chernobyl: effect modifiers (2)

- risk pattern over time

- I-131-related risk persisted more than 20 y after exposure, with no evidence of decrease  
  Brenner et al, 2011

Demidchik, Saenko and Yamashita, 2007
Chernobyl: effect modifiers (3)

• iodine deficiency and iodine supplementation

<table>
<thead>
<tr>
<th>Consumption of potassium iodide</th>
<th>OR at 1 Gy (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Highest two tertiles of soil iodine</td>
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<tr>
<td>No</td>
<td>3.5 (1.8 to 7.0)</td>
</tr>
<tr>
<td>Yes</td>
<td>1.1 (0.3 to 3.6)</td>
</tr>
</tbody>
</table>

Cardis et al, 2005

- in Belarus, diffuse goitre and thyroid enlargement were modifiers of TC risk (Zablotska et al, 2010)
- in Ukraine, data not strong enough to support a modifying effect of iodine deficiency (Brenner et al, 2011)
- indicators of past stable iodine intake are difficult to reconstruct
Chernobyl: effect modifiers (4)

- role of uncertainties in dose estimates on risk
  - relatively small contribution of unshared classical dose error
  - effects of adjusting for dose error were minimal, resulting in changes to risk estimates:
    - in Ukraine between -11% and +7% (Little et al, 2014)
    - In Belarus between -23% and -2% (depending on the method) (Little et al, 2015)
  - new effort to characterise uncertainties in doses and their role on risk estimate in the IARC c-c study
Chernobyl: thyroid exposure in adulthood

- effect of exposure as an adult – uncertain:
  - recent descriptive studies of clean-up workers:
    - Russia (Ivanov et al. 2007) - SIR 3.39 (95% CI 2.73-4.16),
    - Ukraine (Ostroumova et al, 2014) - SIR 3.86 (95 % CI 3.26–4.57)
    - Baltic cohort (Rahu et al, 2013) – PIR 2.76 (95% CI 1.63-4.36)
  - recent studies of residents of contaminated territories >18 y at the time of accident:
    - Russia - no dose-response relationship found in exposed adults (Ivanov et al, 2012)
    - Ukraine – incidence rate in females exposed at ages of 20–49 years was significantly higher in high exposure regions; in males, this tendency was less clear (Fuzik et al, 2011)

- caution:
  - possible surveillance bias
  - no individual dosimetry

Photo: http://www.longshadowofchernobyl.com/photos/chernobyl-victims/

International Agency for Research on Cancer

World Health Organization

ConRad, Munich 2017
Chernobyl: thyroid exposure in adulthood (2)

- 146,000 Chernobyl clean-up workers (liquidators) from Belarus, Estonia, Latvia, Lithuania and Russia
- 107 cases/423 controls
- Individual reconstructed doses, including uncertainty:
  - External – RADRUE method (Kryuchkov et al, 2009)
  - Internal – environmental model validated on available direct thyroid measurements
- Overall median dose – 69mGy
- ERR/100mGy 0.38 (95% CI 0.1-1.09)
  - Similar risks found for external and internal exposures
  - Risk remains significant after excluding tumours Ø1cm or less
  - Impact of uncertainties in doses had modest effect on risk

Kesminiene et al, 2012
Chernobyl and screening

• effect of large scale screening efforts in contaminated areas:
  ❖ absolute rate of thyroid cancer increases in a screened population
  ❖ ERR estimate can be biased upward, if there is a correlation between thyroid dose and frequency of screening
  ❖ BelAm and UkrAm cohort studies provided an estimate of the risk where confounding effect of screening is unlikely (all subjects were screened, regardless of dose)

• however:
  ❔ whether the detection of additional small thyroid cancers affects the excess radiation risks
  ❔ whether these small tumours are induced by radiation to the same extent as large tumours
**worldwide: rise in thyroid cancer incidence**

- estimated number of cases attributable to increased thyroid-gland surveillance:
  - in women:
    - 90% in South Korea;
    - 50% in Japan
  - in men:
    - 70% in South Korea;
    - less than 25% in Japan

- careful data interpretation needed in the context of screening after radiation exposure – Fukushima:
  - risk of overtreatment
  - increased anxiety

*Vaccarella et al, 2016*
summary

• risks following exposure to I-131 are somewhat smaller, but compatible with estimates from external irradiation with latency period 5y and less

• sensitivity to I-131 in children is much greater compared to adults

• I-131-related risk persists nearly 3 decades after Chernobyl accident

• most of observed thyroid malignancies are papillary carcinomas
summary (2)

• 2008 UNSCEAR reported 6,848 cases of thyroid cancer diagnosed amongst those under 18 y in 1986 between 1991 and 2005 in the whole of Belarus and Ukraine and in the 4 most affected regions of the Russian Federation.

• by 2016, more nearly 20,000 thyroid cancer cases had been diagnosed in this group (unpublished data).

• a fraction of these is attributable to radioiodine intake in 1986.
there is more to be learned about thyroid cancer…

• about the impact of:
  - gender, age at exposure, including in adulthood
  - stable iodine intake
  - increased surveillance
  - …

• there is a need for studies to better understand natural history of thyroid cancer (progression and regression of thyroid tumours over life span)

• efforts to characterise mutational signature of the radiation-induced thyroid cancer genomes and to provide insights into radiation carcinogenesis underway
Thank you!